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(54) Process for the desilylation of a 4-silyloxy-tetrahydro-pyran-2-one.

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EP-A- 0 331 240
EP-A- 0 349 063
DE-A- 3 530 789

SYNTHETIC COMMUNICATIONS, 9(4), 295-299
(1979) US-A-4 733 003

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Description

Hypercholesterolemia is known to be one of the prime risk factors for ischemic cardiovascular disease, such as arteriosclerosis. Bile acid sequestrants have been used to treat this condition; they seem to be moderately effective but they must be consumed in large quantities, i.e. several grams at a time, and they are not very palatable.

MEVACOR® (lovastatin), now commercially available is one of a group of very active antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by inhibiting the enzyme, HMG-CoA reductase. In addition to the natural fermentation products, mevastatin and lovastatin, there are a variety of semi-synthetic and totally synthetic analogs thereof.

The preparation of the semi-synthetic and totally synthetic analogs generally involves silyl group protection of the 4-hydroxy group on these mevalonic acid derivatives. The silyl protecting group must eventually be removed, typically in the last step of the synthetic route. In prior efforts, the desilylation has been accomplished with tetra-n-butylammonium fluoride or dilute HF or methanesulfonic acid. The fluoride-based desilylation procedures were problematic on a large scale due to the corrosive properties of the reagent on pilot plant equipment. The methanesulfonic acid desilylation procedure was undesirable because it caused opening of the lactone moiety, which necessitated the introduction of a relactonization step.

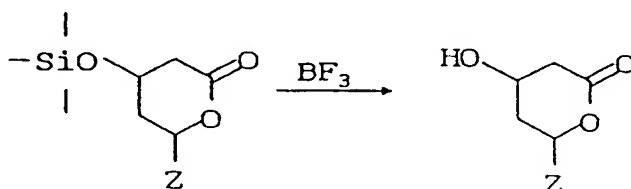
European patent specification no. 0 349 063 discloses deprotection using either tetra-n-butylammonium fluoride in acetic acid/THF or with hydrogen fluoride in pyridine. European patent specification no. 0 331 240 discloses deprotection by treatment with HF in acetonitrile. Similarly, German patent specification no. 3 530 798 discloses deprotection with HF in acetonitrile or with tetrabutylammonium fluoride in acetic acid/THF.

D. R. Kelly et. al. in Synthetic Communications, 9 295 (1979) (referred to in T. Greene et. al., "Protective Groups in Organic Synthesis", 2nd edition, (1991) pages 77-83) discloses cleavage of the t-butyldimethylsilyl hydroxyl protecting group with boron trifluoride etherate at 0 to 25° celcius, however, under these conditions elimination is observed where the product is a conjugated system (see especially the reaction of the alkene (3a) to give the diene (4) on pages 296 and 297).

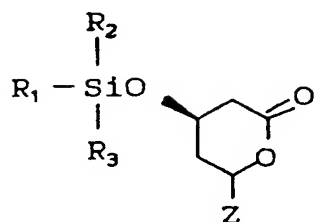
The present invention introduces a novel desilylation procedure which has the advantage of increased yield over the prior procedures and increased ease of operation. The process of the present invention is not corrosive to pilot plant equipment and does not cause reactions at the lactone carbonyl.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a process for the removal of a silyl protecting group from the 4-hydroxy group of a tetrahydro-pyran-2-one moiety.



wherein Z represents a lipophilic group such as a polyhydronaphthyl moiety or an aryl or heteroaryl moiety. More particularly the present invention, in its application to the preparation of HMG-CoA reductase inhibitors, is a process for the desilylation of a compound (I):



(I)

wherein

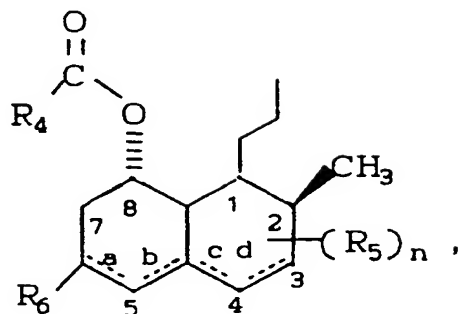
 R_1 , R_2 , and R_3 are each independently selected from:

- a) C_1 - C_4 alkyl;
- b) phenyl;
- c) phenyl- CH_2 -;
- d) p - CH_3 -phenyl- CH_2 ; and

 Z

is selected from:

- a)



wherein:

 R_4 is C_1 - C_{10} alkyl; R_5 is selected from:

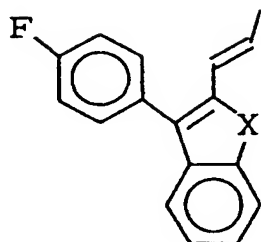
- a) C_1 - C_3 alkyl;
- b) hydroxy;
- c) oxo;
- d) C_1 - C_3 alkyl substituted with hydroxy;

 n is 0, 1 or 2; R_6 is selected from:

- a) hydrogen;
- b) C_1 - C_3 alkyl;
- c) C_1 - C_3 alkyl substituted with hydroxy; or
- d) hydroxy; and

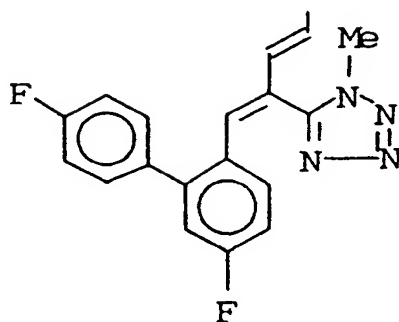
a,b,c, and d are all single bonds or a and c are double bonds or b and d are double bonds or one of a,b,c,d is a double bond;

b)

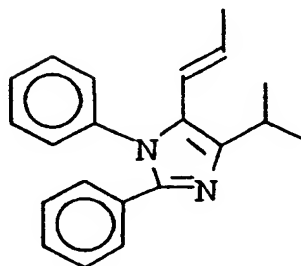


wherein X is $\text{NCH}(\text{CH}_3)_2$ or $\text{C}(\text{CH}_2)_4$

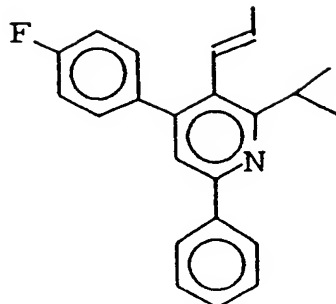
c)



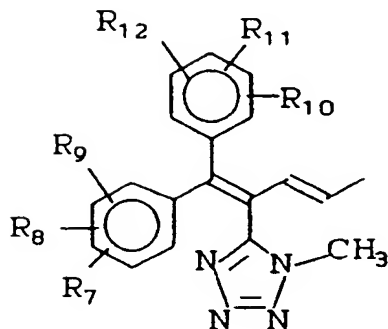
d)



e)



f)



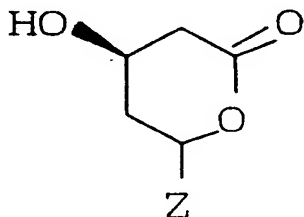
wherein

R₇ and R₁₀ are each independently selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy or trifluoromethyl;

R₈, R₉, R₁₁, R₁₂ are each independently selected from Hydrogen, halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy;

which comprises:

contacting of a compound of formula (I) in a polar aprotic solvent such as acetonitrile, dichloromethane, tetrahydrofuran, ethyl acetate, or a mixture thereof; with boron trifluoride etherate, at a temperature of about -10° to 24°C for about 15 minutes to one hour, to yield a compound of formula (II):

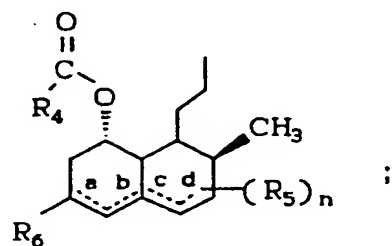


(II)

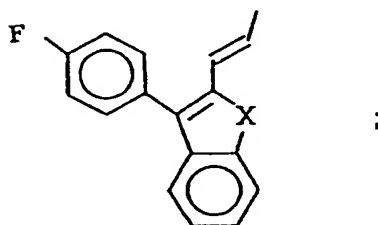
The preferred silyloxy protecting groups are trimethylsilyloxy, triethylsilyloxy, isopropyl dimethylsilyloxy, t-butyl dimethylsilyloxy, (triphenylmethyl)-dimethylsilyloxy, t-butyl diphenylsilyloxy, methyldiisopropylsilyloxy, tribenzylsilyloxy, tri-p-xylylsilyloxy, triisopropylsilyloxy and triphenylsilyloxy. Most preferred are t-butyl dimethylsilyloxy and trimethylsilyloxy.

The moiety Z may be any lipophilic group which is compatible with the boron trifluoride reactant.
 Preferably Z is selected from:

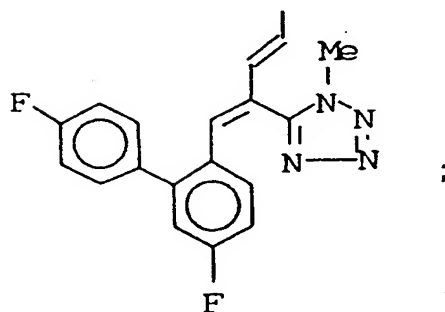
(a)



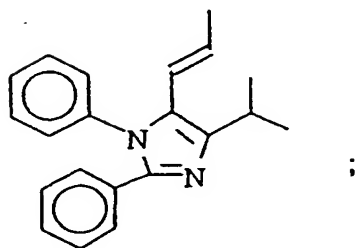
or
 (b)



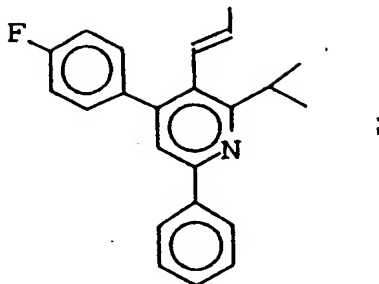
(c)



(d)

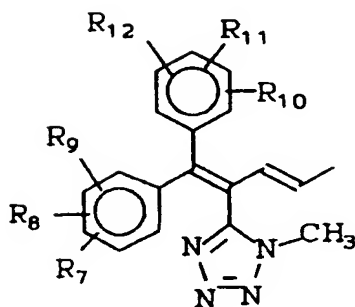


(e)



or

(f)



A preferred use of the present invention is the preparation of compounds (II) wherein Z is the polyhydronaphthyl group (a) and R₄ is 2-butyl or 2, 2-dimethylpropyl, and R₆ is hydrogen, methyl, hydroxy or hydroxymethyl and n is 0 or 1, wherein, when n is 1, R₅ is hydroxy in the 5-position or oxo in the 3-position or (1-hydroxyethyl) in the 7-position, and b and d are double bonds or a and c are double bonds or a b c d are single bonds provided that when R₆ is hydroxy, b and d are double bonds and when R₅ is 3-oxo a and c are double bonds, and, when R₅ is hydroxy, a, b, c and d are all single bonds.

The most preferred use is in the preparation of Compounds (II) wherein

- (a) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 0 and b and d are double bonds;
- (b) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 1, R₅ is 5-OH, a, b, c, d are all single bonds;
- (c) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 1, R₅ is 3-oxo, a and c are double bonds;
- (d) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 1, R₅ is (1-hydroxyethyl) in the 7-position, b and d are double bonds;
- (e) R₄ is 2-butyl, R₆ is CH₃, n is 0 and b and d are double bonds;
- (f) R₄ is 2,2-dimethylpropyl, R₆ is CH₂OH, n is 0 and b and d are double bonds.

The present invention comprises desilylation at the 4-hydroxy group of a tetrahydro-pyran-2-one moiety. Specifically the process comprises the treatment of a compound (I) with boron trifluoride in a polar aprotic solvent such as CH₃CN, THF, CH₂Cl₂, EtoAc, or a mixture thereof, at a temperature of about -10° to +25° C.

The preferred solvent is CH₃CN at a temperature of about 0° to 5° C. Approximately equivalent amounts of (I) to BF₃ are treated together. After treatment with BF₃ the reaction mixture is quenched with aqueous NaHCO₃, the phases, separated and the organic layer washed with aqueous NaCl, concentrated, distilled, and finally allowed to crystallize to product (II).

Hydroxyl groups contained in compounds of formula (I) may be silylated according to the procedures in U.S. patent 4,444,784.

Compounds of formula (I) may contain, in the Z moiety, a hydroxyl group which may be protected as a silyloxy group. In this case the mole ratio of BF₃ to compound (I) can be increased so that all silyloxy

protecting groups are removed in one step. It should be understood that, where R_5 or R_6 substituent groups contain hydroxy, protected hydroxy such as silyloxy are also included on compounds of formula (I) within the present invention.

5 EXAMPLE 1

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S),6(R)-dimethyl-5(R)-hydroxy-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6,-tetrahydro-2H-pyran-2-one.

10 A dry two liter, three neck flask equipped with an overhead stirrer, a nitrogen inlet, a temperature probe, and a septum was charged with 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S),6(R)-dimethyl-5(R)-hydroxy-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6,-tetrahydro-2H-pyran-2-one, (50.0 g, 0.0904 mole) and acetonitrile (500 mL). The clear colorless solution was cooled to 0-3°C. Boron trifluoride etherate (12.5 mL, 0.102 mole,) was added by syringe over 2.0 min, and the
15 resulting pale yellow solution was stirred at 0-3°C until the reaction was complete (about 30 min).

The reaction was quenched by the addition of NaHCO_3 solution (41.4 mg/mL, aqueous, 300 mL,) over 5-7 min while keeping the temperature $\leq 10^\circ\text{C}$. The mixture was then vigorously stirred for 1.0 h while being allowed to warm to 20°C . The phases were separated, and the pale yellow organic phase washed with NaCl solution (saturated, aqueous, 300 mL). The organic layer was concentrated in vacuo to one half
20 volume (internal temp. $\leq 30^\circ\text{C}$), then switched over to isopropyl acetate by dilution with isopropyl acetate followed by distillation to a final volume of 1250 mL. The solution was washed with deionized water (750 mL) and then transferred to a two liter, three neck flask equipped with an overhead stirrer and a distillation apparatus. The residual water was removed by azeotropic vacuum distillation with isopropyl acetate (500 mL, internal temp. $\leq 30^\circ\text{C}$) to a KF $\leq 500 \mu\text{g/mL}$. The volume was adjusted to 280 mL, and the solution was
25 seeded, if necessary. The product was allowed to crystallize at 25°C for 30 min. Hexanes (840 mL) were then added slowly over 1.0 h. The mixture was aged at 25°C for 30 min and then at -5°C overnight (17 h). The product was collected by filtration on a sintered glass funnel, and the crystals washed with cold (-10°C) isopropyl acetate in hexanes 25 v/v % (2 x 30 mL). The white crystalline solids were dried in vacuo at 25°C with a nitrogen sweep to give the title compound in a yield of 87%.

30 EXAMPLES 2-5

Employing the procedure substantially as described in Example 1, but substituting for the silylated alcohol therein an approximately equimolar amount of the compounds (I) described in table I there are
35 prepared the desilylated products (II) also described in table I.

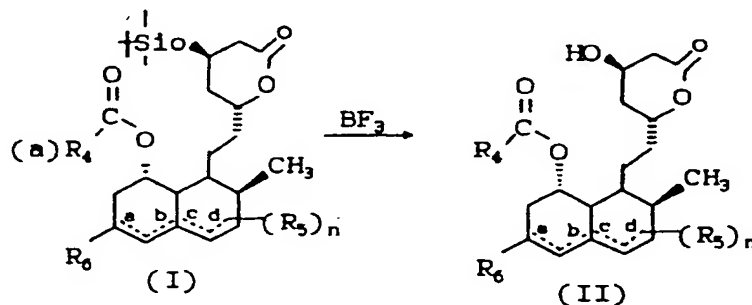
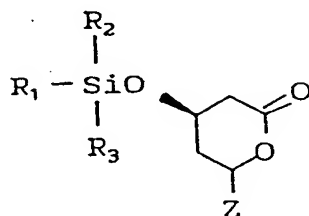


TABLE I

| Example | R_4 | R_6 | n | R_5 | Double bond |
|---------|--------------------|-----------------|---|--|-------------|
| 2 | 2,2-dimethylpropyl | CH ₃ | 0 | | b, d |
| 3 | 2-butyl | CH ₃ | 0 | | b, d |
| 4 | 2,2-dimethylpropyl | CH ₃ | 1 | 3-C=O | a, c |
| 5 | 2,2-dimethylpropyl | CH ₃ | 1 | $\begin{array}{c} \text{H} \\ \\ 7-\text{C}-\text{CH}_3 \\ \\ \text{OH} \end{array}$ | b, d |

Claims

1. A process for the desilylation of a compound (I)



(I)

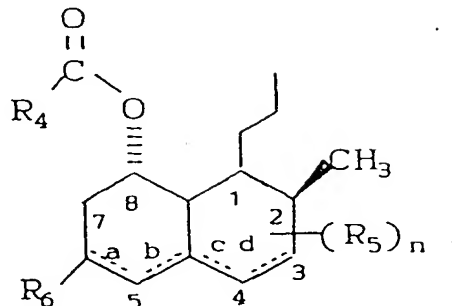
wherein

R_1 , R_2 , and R_3 are each independently selected from:

- a) C₁ - C₄ alkyl;
- b) phenyl;
- c) phenyl-CH₂-;
- d) p-CH₃-phenylCH₂;

Z is selected from:

- a)



wherein

R_4 is C_1 - C_{10} alkyl;

R_5 is selected from:

a) C_1 - C_3 alkyl;

b) hydroxy;

c) oxo

d) C_1 - C_3 alkyl substituted with hydroxy;

n is 0, 1 or 2;

R_6 is selected from:

a) hydrogen

b) C_1 - C_3 alkyl;

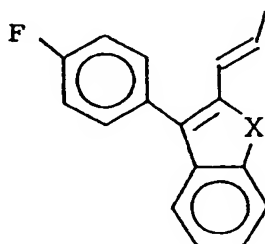
c) C_1 - C_3 alkyl substituted with hydroxy

d) hydroxy; and

a,b,c, and d are all single bonds or a and c are double bonds or b and d are double bonds or one of

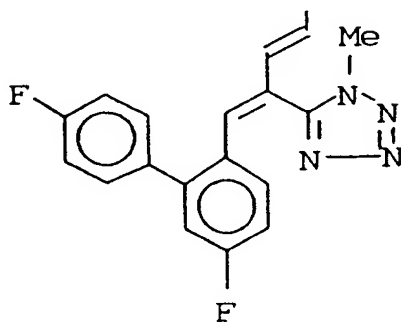
a,b,c,d is a double bond;

b)

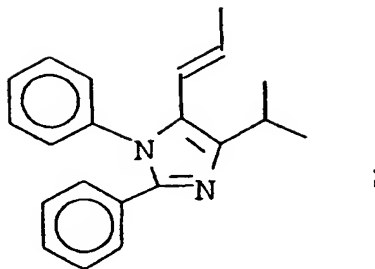


wherein X is $NCH(CH_3)_2$ or $C(CH_2)_4$

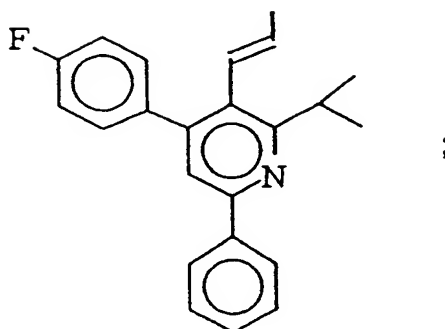
c)



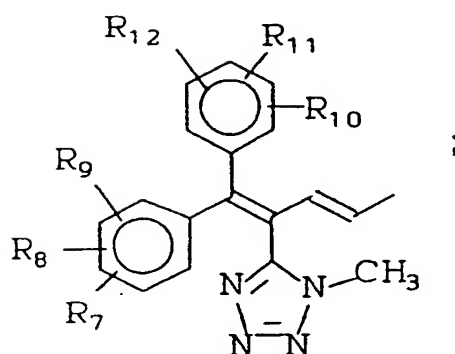
d)



e)



f)



wherein

R_7 and R_{10}

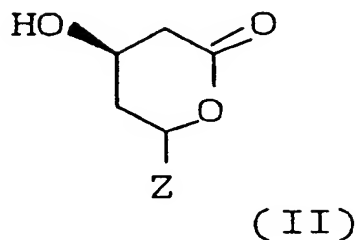
are each independently selected from hydrogen, halogen, C_1-4 alkyl, C_1-4 alkoxy or trifluoromethyl;

R_8 , R_9 , R_{11} , R_{12}

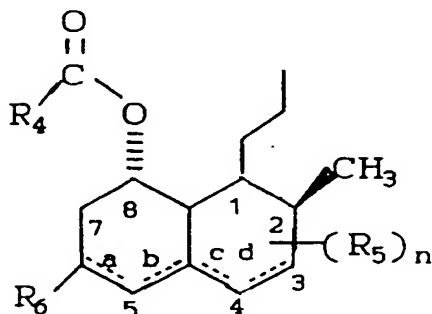
are each independently selected from Hydrogen, halogen, C_1-4 alkyl, or C_1-4 alkoxy;

which comprises:

contacting a compound of formula (I) in a solvent selected from acetonitrile, CH_2Cl_2 , THF, ethyl acetate, or a mixture thereof; with boron trifluoride etherate at a temperature of about -10 to $24^\circ C$ to yield a compound of formula (II):



2. The process of Claim 1 wherein the silyloxy protecting group is selected from: trimethylsilyloxy, triethylsilyloxy, isopropylidimethylsilyloxy, t-butylidimethylsilyloxy, (triphenylmethyl)-dimethylsilyloxy, t-butylidiphenylsilyloxy, methyldiisopropylsilyloxy, tribenzylsilyloxy, tri-p-xylylsilyloxy, triisopropylsilyloxy or triphenylsilyloxy.
3. The process of Claim 2 wherein the silyloxy protecting group is tert-butylidimethylsilyloxy or trimethylsilyloxy.
4. The process of Claim 1 wherein the group Z is:
 - a)



5. A process according to Claim 4 wherein R₄ is 2-butyl or 2,2-dimethylpropyl and R₆ is H, methyl, hydroxy or hydroxymethyl.
6. A process according to Claim 5 where n is 0 or 1.
7. A process according to Claim 6 wherein the solvent is acetonitrile.
8. A process according to Claim 7 wherein n is 1; and
 - a) R₅ is 5-OH, a, b, c and d are single bonds;
 - b) R₅ is 3-oxo, a and c are double bonds or c is a double bond; or
 - c) R₅ is 7-(1-hydroxyethyl), b and d are double bonds;
 provided that when R₆ is OH, b and d are double bonds or c is a double bond or a, b, c and d are single bonds.
9. The process according to Claim 7 wherein the Compound (II) prepared is selected from:
 - a) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 0 and b and d are double bonds;
 - b) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 1, R₅ is 5-OH, a, b, c and d are all single bonds;
 - c) R₄ is 2,2-dimethylpropyl, R₆ is CH₃, n is 1, R₅ is 3-oxo and a and c are double bonds;

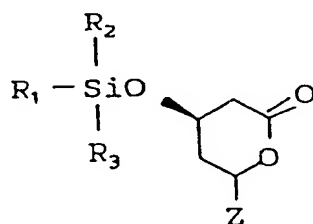
d) R_4 is 2,2-dimethylpropyl, R_6 is CH_3 , n is 1, R_5 is 7-(1-hydroxyethyl) and \underline{b} and \underline{d} are double bonds.

e) R_4 is 2,2-dimethylpropyl, R_6 is CH_2OH , n is 0, and \underline{b} and \underline{d} are double bonds;

f) R_4 is 2-butyl, R_6 is CH_3 , n is 0 and \underline{b} and \underline{d} are double bonds.

Patentansprüche

1. Verfahren zur Desilylierung einer Verbindung (I)



(I)

worin

R_1 , R_2 und R_3

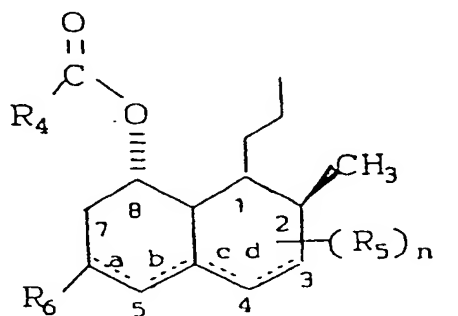
jeweils unabhängig ausgewählt werden aus

- a) C_1 - C_4 -Alkyl,
- b) Phenyl,
- c) Phenyl- CH_2 -,
- d) p- CH_3 -Phenyl- CH_2 ,

Z

ausgewählt wird aus

- a)



worin

R_4

für C_1 - C_{10} -Alkyl steht,

R_5

ausgewählt wird aus

- a) C_1 - C_3 -Alkyl,
- b) Hydroxy,
- c) Oxo,
- d) C_1 - C_3 -Alkyl, substituiert mit Hydroxy,

n

0, 1 oder 2 bedeutet,

R_6

ausgewählt wird aus

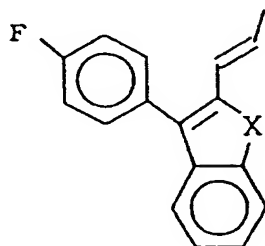
- a) Wasserstoff,
- b) C_1 - C_3 -Alkyl,

c) C₁-C₃-Alkyl, substituiert mit Hydroxy,

d) Hydroxy und

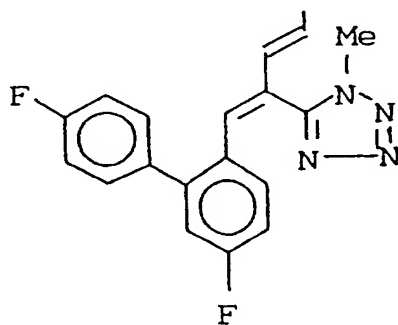
a, b, c und d alles Einfachbindungen darstellen oder a und c Doppelbindungen darstellen oder b und d Doppelbindungen darstellen oder eines von a, b, c und d eine Doppelbindung darstellt,

b)

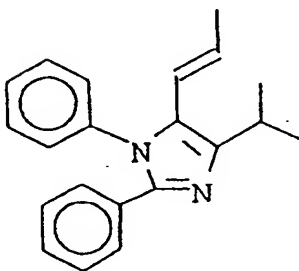


worin X für NCH(CH₃)₂ oder C(CH₂)₄ steht,

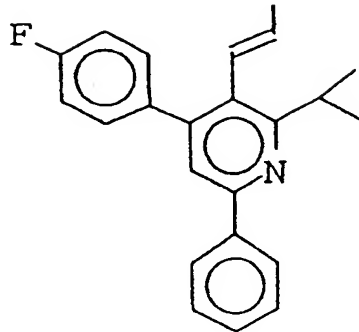
c)



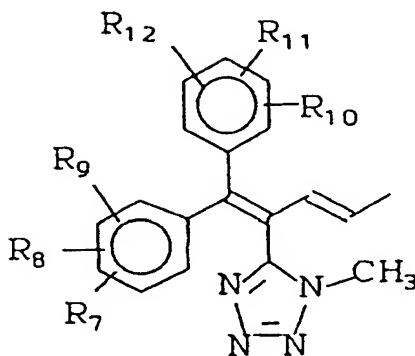
d)



e)



f)

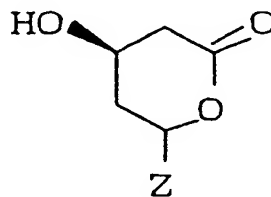


worin

R₇ und R₁₀ jeweils unabhängig ausgewählt werden aus Wasserstoff, Halogen, C₁-4-Alkyl, C₁-4-Alkoxy oder Trifluormethyl,
 R₈, R₉, R₁₁, R₁₂ jeweils unabhängig ausgewählt werden aus Wasserstoff, Halogen, C₁-4-Alkyl oder C₁-4-Alkoxy,

welches umfaßt:

Zusammenbringen einer Verbindung der Formel (I) in einem Lösungsmittel, ausgewählt aus Acetonitril, CH₂Cl₂, THF, Ethylacetat oder einem Gemisch davon, mit Bortrifluoridetherat bei einer Temperatur von etwa -10 bis 24 °C, so daß sich eine Verbindung der Formel (II) ergibt

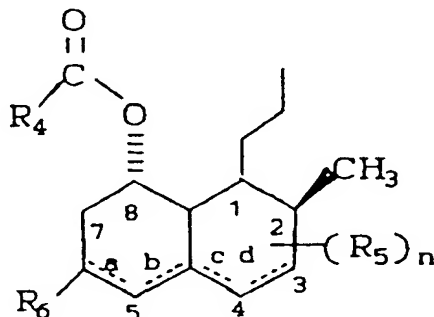


(II)

2. Verfahren nach Anspruch 1, worin die Silyloxy-Schutzgruppe ausgewählt wird aus Trimethylsilyloxy, Triethylsilyloxy, Isopropylidimethylsilyloxy, t-Butyldimethylsilyloxy, (Triphenylmethyl)-dimethylsilyloxy, t-

Butyldiphenylsilyloxy, Methyldiisopropylsilyloxy, Tribenzylsilyloxy, Tri-p-xylylsilyloxy, Triisopropylsilyloxy oder Triphenylsilyloxy.

3. Verfahren nach Anspruch 2, bei dem die Silyloxy-Schutzgruppe tert-Butyldimethylsilyloxy oder Trimethylsilyloxy ist.
4. Verfahren nach Anspruch 1, bei dem die Gruppe Z
 - a)

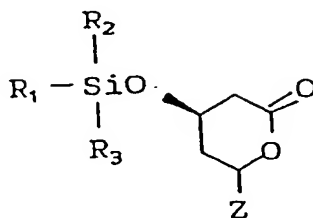


darstellt.

5. Verfahren nach Anspruch 4, bei dem R_4 für 2-Butyl oder 2,2-Dimethylpropyl steht und R_6 H, Methyl, Hydroxy oder Hydroxymethyl bedeutet.
6. Verfahren nach Anspruch 5, bei dem n für 0 oder 1 steht.
7. Verfahren nach Anspruch 6, bei dem das Lösungsmittel Acetonitril ist.
8. Verfahren nach Anspruch 7, bei dem n 1 bedeutet und
 - a) R_5 für 5-OH steht a, b, c und d Einfachbindungen sind,
 - b) R_5 für 3-Oxo steht, a und c Doppelbindungen darstellen oder c für eine Doppelbindung steht oder
 - c) R_5 7-(1-Hydroxyethyl) bedeutet, b und d Doppelbindungen darstellen,
 mit der Maßgabe, daß, wenn R_6 für OH steht, b und d Doppelbindungen sind oder c eine Doppelbindung ist oder a, b, c und d Einfachbindungen sind.
9. Verfahren nach Anspruch 7, bei dem die hergestellte Verbindung (II) aus dem Folgendem ausgewählt wird:
 - a) R_4 steht für 2,2-Dimethylpropyl, R_6 steht für CH_3 , n bedeutet 0 und b und d stellen Doppelbindungen dar,
 - b) R_4 steht für 2,2-Dimethylpropyl, R_6 steht für CH_3 , n bedeutet 1, R_5 bedeutet 5-OH, a, b, c und d stellen alles Einfachbindungen dar,
 - c) R_4 steht für 2,2-Dimethylpropyl, R_6 steht für CH_3 , n bedeutet 1, R_5 bedeutet 3-Oxo und a und c stellen Doppelbindungen dar,
 - d) R_4 steht für 2,2-Dimethylpropyl, R_6 steht für CH_3 , n bedeutet 1, R_5 bedeutet 7-(1-Hydroxyethyl) und b und d stellen Doppelbindungen dar,
 - e) R_4 steht für 2,2-Dimethylpropyl, R_6 steht für CH_2OH , n bedeutet 0 und b und d stellen Doppelbindungen dar,
 - f) R_4 steht für 2-Butyl, R_6 steht für CH_3 , n bedeutet 0 und b und d stellen Doppelbindungen dar.

Revendications

1. Procédé pour la désilylation d'un composé (I)



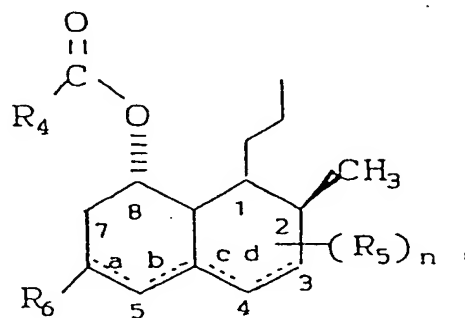
(I)

dans lequel R₁, R₂ et R₃ sont chacun indépendamment choisis parmi :

- a) un groupe alkyle en C₁₋₄ ;
- b) un groupe phényle ;
- c) un groupe phényl-CH₂- ;
- d) un groupe p-CH₃-phényl-CH₂ ;

Z est choisi parmi:

- a)



où

R₄ est un groupe alkyle en C₁₋₁₀ ;

R₅ est choisi parmi :

- a) un groupe alkyle en C₁₋₃ ;
- b) un groupe hydroxy ;
- c) un groupe oxo ;
- d) un groupe alkyle en C₁₋₃ substitué par un groupe hydroxy ;

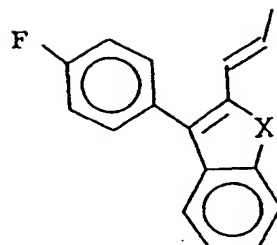
n vaut 0, 1 ou 2 ;

R₆ est choisi parmi :

- a) un atome d'hydrogène ;
- b) un groupe alkyle en C₁₋₃ ;
- c) un groupe alkyle en C₁₋₃ substitué par un groupe hydroxy ;
- d) un groupe hydroxy ; et

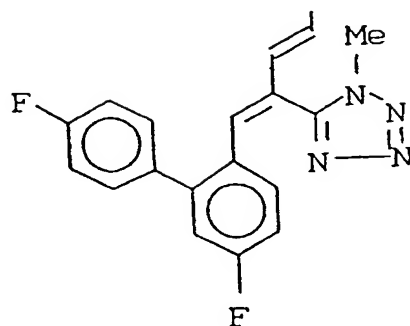
a, b, c et d sont tous des liaisons simples ou a et c sont des liaisons doubles ou b et d sont des liaisons doubles ou l'un d'entre a, b, c, d est une liaison double ;

b)

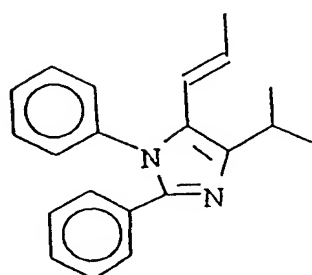


où X est $\text{NCH}(\text{CH}_3)_2$ ou $\text{C}(\text{CH}_2)_4$

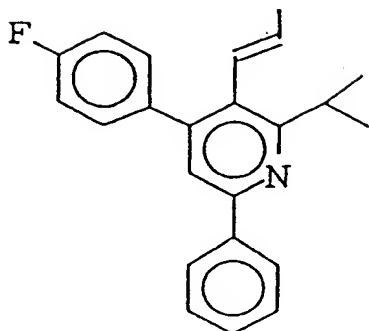
c)



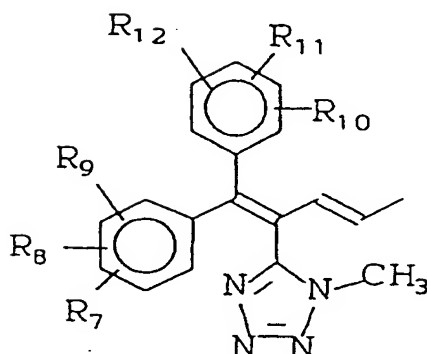
d)



e)



f)

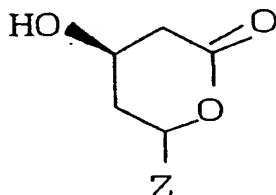


où R₇ et R₁₀ sont chacun indépendamment choisis parmi un atome d'hydrogène ou d'halogène ou un groupe alkyle en C₁₋₄, alcoxy en C₁₋₄ ou trifluorométhyle ;

R₈, R₉, R₁₁, R₁₂ sont chacun indépendamment choisis parmi un atome d'hydrogène ou d'halogène ou un groupe alkyle en C₁₋₄ ou alcoxy en C₁₋₄ ;

qui comprend :

la mise en contact d'un composé de formule (I) dans un solvant choisi parmi l'acétonitrile, CH₂Cl₂, THF, l'acétate d'éthyle ou un de leurs mélanges, avec l'éthérate de trifluorure de bore, à une température d'environ - 10 à 24 °C pour donner un composé de formule (II) :



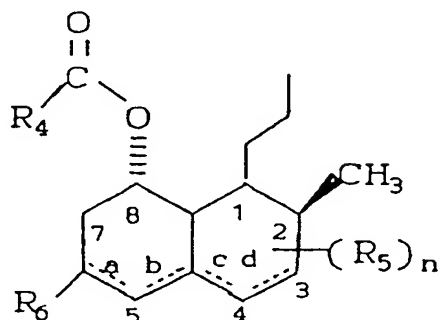
(II)

2. Procédé selon la revendication 1, dans lequel le groupe protecteur silyloxy est choisi parmi les groupes : triméthylsilyloxy, triéthylsilyloxy, isopropyl diméthylsilyloxy, t-butyl diméthylsilyloxy, (triphenylmethyl)-diméthylsilyloxy, t-butyl diphenylsilyloxy, méthyl diisopropylsilyloxy, tribenzylsilyloxy, tri-p-xylylsilyloxy, triisopropylsilyloxy ou triphenylsilyloxy.

3. Procédé selon la revendication 2, dans lequel le groupe protecteur silyloxy est le groupe tert-butyldiméthylsilyloxy ou triméthylsilyloxy.

4. Procédé selon la revendication 1, dans lequel le groupe Z est :

a)



5. Procédé selon la revendication 4, dans lequel R_4 est un groupe 2-butyle ou 2,2-diméthylpropyle et R_6 est H ou un groupe méthyle, hydroxy ou hydroxyméthyle.

6. Procédé selon la revendication 5, dans lequel n vaut 0 ou 1.

7. Procédé selon la revendication 6, dans lequel le solvant est l'acétonitrile.

8. Procédé selon la revendication 7, dans lequel n vaut 1 ; et

a) R_5 est 5-OH, a, b, c, d sont des liaisons simples ;

b) R_5 est un groupe 3-oxo, a et c sont des liaisons doubles ou c est une liaison double ; ou

c) R_5 est un groupe 7-(1-hydroxyéthyle), b et d sont des liaisons doubles

à condition que lorsque R_6 est OH, b et d sont des liaisons doubles ou c est une liaison double ou a, b, c, d sont des liaisons simples.

9. Procédé selon la revendication 7, dans lequel le composé (II) préparé est choisi parmi:

a) R_4 est un groupe 2,2-diméthylpropyle, R_6 est CH_3 , n vaut 0 et b et d sont des liaisons doubles ;

b) R_4 est un groupe 2,2-diméthylpropyle, R_6 est CH_3 , n vaut 1, R_5 est 5-OH, a, b, c et d sont tous des liaisons simples ;

c) R_4 est un groupe 2,2-diméthylpropyle, R_6 est CH_3 , n vaut 1, R_5 est un groupe 3-oxo et a et c sont des liaisons doubles ;

d) R_4 est un groupe 2,2-diméthylpropyle, R_6 est CH_3 , n vaut 1, R_5 est un groupe 7-(1-hydroxyéthyle) et b et d sont des liaisons doubles ;

e) R_4 est un groupe 2,2-diméthylpropyle, R_6 est CH_2OH , n vaut 0 et b et d sont des liaisons doubles ;

f) R_4 est un groupe 2-butyle, R_6 est CH_3 , n vaut 0 et b et d sont des liaisons doubles.